**Amendments to the Specification:**

On page 3, please replace paragraph **[0009]** with the following amended paragraph:

**[0009]** This invention pertains to the development of a novel molecular sensing apparatus (biosensor) and to methods of use thereof. In preferred embodiments, ~~the particular,~~ the sensing apparatus comprises a first electrode, a second electrode, an insulator between the first electrode and the second electrode; and a binding agent (*e.g.* a biological macromolecule) connecting the first electrode and the second electrode. In particularly preferred embodiments, the binding agent is attached to the electrode in a manner that permits charge to flow from the electrode to the binding agent or from the binding agent to the electrode. Preferred binding agents include, but are not limited to, biological macromolecules (*e.g.* a nucleic acid, a protein, a polysaccharide, a lectin, a lipid, *etc.*) with a nucleic acid being most preferred. While the nucleic acid can be essentially any length, preferred nucleic acids range in length from about 5 nucleotides to about 5,000 nucleotides, more preferably from about 8 nucleotides to about 1,000 nucleotides or 500 nucleotides, still more preferably from about 10 nucleotides to about 300 nucleotides, and most preferably from about 15, 20, 25, 30 or 50 nucleotides to about 100 nucleotides or 150 nucleotides in length. Typically, the nucleic acid is of sufficient length to specifically hybridize to a target nucleic acid in a complex population of nucleic acids (*e.g.* total genomic DNA) under stringent conditions.

On page 7, please replace paragraph **[0023]** with the following amended paragraph:

**[0023]** In still another embodiment, this invention provides a method of detecting an analyte. The method involves i) providing a molecular sensing apparatus comprising a first electrode and a second electrode separated by an insulator where said first electrode has a biological macromolecule attached thereto; ii) contacting the attached macromolecule with said analyte whereby said analyte binds to said macromolecule thereby forming a macromolecule/analyte complex; iii) placing a charge on said second electrode to attract a portion of said bound analyte to said second electrode where said second analyte is bound to the second electrode such that the macromolecule/analyte complex forms a connection between the first electrode and the second electrode; and iv) detecting the connection between said first and said second electrode. In certain embodiments, the providing comprises: contacting the first electrode with a first solution comprising the biological macromolecule; and placing a charge on the first electrode whereby the charge attracts the

biological macromolecule to the electrode and the biological macromolecule attaches to the electrode. Where multiple electrode pairs are present, the method can involve repeating these steps for each electrode pair. The "placing a charge" can, optionally involve placing a charge on the first electrode opposite to the charge on the second electrode. In certain embodiments, the "detecting" comprises detecting an electromagnetic property selected from the group consisting of direct electric current, alternating electric current, permittivity, resistivity, electron transfer, electron tunneling, electron hopping, electron transport, electron conductance, voltage, electrical impedance, signal loss, dissipation factor, resistance, capacitance, inductance, magnetic field, electrical potential, charge, and magnetic potential. Preferred macromolecules, electrodes, electrode configurations, insulators, measurement devices, circuits, and the like, include, but are not limited to those described above.

On page 8, please replace paragraph **[0025]** with the following amended paragraph:

**[0025]** This invention provides still another method of detecting an analyte. The method involves i) providing a molecular sensing apparatus comprising a first electrode and a second electrode separated by an insulator where a biological macromolecule forms a connection between the first electrode and the second electrode; ii) detecting the connection between ~~said~~ the first and the second electrode; iii) contacting the biological macromolecule (binding agent) with the analyte whereby the analyte binds to the macromolecule thereby forming a macromolecule/analyte complex; and iv) detecting a difference in the connection between the first electrode and ~~said~~ the second electrode. In certain embodiments, the "contacting" comprises placing a charge on the first and/or the second electrode whereby the charge attracts the analyte to the biological macromolecule. In certain embodiments, the "providing" comprises contacting the first electrode with a first solution comprising the biological macromolecule; and placing a charge on the first electrode whereby the charge attracts the biological macromolecule to the electrode and the biological macromolecule attaches to the electrode; and placing a charge on the second electrode to attract a portion of the bound macromolecule to the second electrode where the macromolecule is bound to the second electrode such that ~~said~~ the macromolecule forms a connection between the first electrode and said second electrode. In certain embodiments, the "placing a charge" comprises placing a charge on ~~said~~ the first electrode opposite to the charge on ~~said~~ the second electrode. The ~~"detecting"~~ "detecting" can comprise detecting an electromagnetic property selected from the group consisting of direct electric current, alternating electric current, permitivity, resistivity, electron transfer, electron tunneling, electron hopping, electron transport, electron conductance, voltage, electrical impedance, signal loss,

dissipation factor, resistance, capacitance, inductance, magnetic field, electrical potential, charge and magnetic potential. In particularly preferred embodiments, the biological macromolecule is attached to ~~said~~ the first electrode by an electrically conductive linker. In certain embodiments, the binding agent is a nucleic acid and the analyte is a protein or a protein complex. Preferred macromolecules, electrodes, electrode configurations, insulators, measurement devices, circuits, and the like, include, but are not limited to those described above.

On page 15, please replace paragraph **[0054]** with the following amended paragraph:

**[0054]** This invention pertains to ~~a~~ novel sensors (biosensors) that are useful for detecting a wide range of analytes. The sensors utilize a binding agent (*e.g.* a biomolecule) to specifically bind to one or more target analytes and thereby confer specificity and selectivity. In preferred embodiments, the binding agent (*e.g.* biomolecule) spans a gap between two electrodes. Binding of the target analyte changes conductivity, or other electrical properties, of the sensor thereby facilitating ready detection of the binding event and thus detection and/or quantitation of the bound analyte. Because the biosensors of this invention provide a change in conductance or charge flow when bound by the target analyte, they are easily read using electronic/electrochemical means and do not require the use of detectable labels.

On page 16, please replace paragraph **[0055]** with the following amended paragraph:

**[0055]** One embodiment of a basic ~~the~~ biosensor (molecular sensing apparatus) of this invention is schematically illustrated in Figure 1. The sensor comprises a first electrode **10**, a second electrode **12**, and a binding agent (*e.g.* biomolecule) **14** spanning the gap between the two electrodes. The two electrodes can be separated by an air gap, however, in preferred embodiments, the electrodes are separated by a spacer **16** (*e.g.* an insulator, a ~~dialectric~~ dielectric, or a semiconductor). The binding agent **14** can be directly bound to the electrodes or it can be coupled to the first electrode **10** and/or the second electrode **12** through one or more linkers or functional groups **18**. The binding agent **14** is attached to the electrodes in a manner that leaves sufficient area of the sensor molecule free to bind with its "cognate" target molecule **20** (the target analyte).

On page 17, please replace paragraph **[0060]** with the following amended paragraph:

**[0060]** Intercalating reagents that change the conductivity of a biomolecule or molecular complex are well known to those of skill in the art. Such intercalators include, but are not limited to redox-active cations ~~(e.g. $Ru(NH_3)_6^{3+}$~~ (*e.g.* $Ru(NH_3)_6^{3+}$) and various transition metal/ligand complexes. Transition metals are those whose atoms have an incomplete shell of electrons. Suitable transition metals for use in the invention include, but are not limited to, cadmium (Cd), magnesium (Mg), copper (Cu), cobalt (Co), palladium (Pd), zinc (Zn), iron (Fe), ruthenium (Ru), rhodium (Rh), osmium (Os), rhenium (Re), ~~platinium~~ platinum (Pt), scandium (Sc), titanium (Ti), ~~Vanadium~~ vanadium (V), chromium (Cr), manganese (Mn), nickel (Ni), ~~Molybdenum~~ molybdenum (Mo), technetium (Tc), tungsten (W), and iridium (Ir). That is, the first series of transition metal, the platinum metals (Ru, Rh, Pd, Os, Ir and Pt), along with Re, W, Mo and Tc, are preferred. Particularly preferred are ruthenium, rhenium, osmium, ~~platinium~~ platinum and iron.

On page 19, please replace paragraph **[0070]** with the following amended paragraph:

**[0070]** The electrodes comprising ~~and~~ an electrode pair (sensor element) can be of any convenient dimension. In preferred embodiments, the electrodes comprising an electrode pair are spaced such that the analyte and/or the analyte/binding agent combination span the gap between the electrodes. In certain embodiments, the electrodes are separated by a distance ranging from about of 1 Angstrom to about $10^{10}$ Angstroms, preferably from about 10 Angstroms to about $10^5$ Angstroms, more preferably from about 25 Angstroms to about $10^4$ Angstroms, and most preferably from about 40 Angstroms to about ~~angstroms~~ Angstroms. Preferred interelectrode spacings are less than about 200 ~~angstroms~~ Angstroms, preferably less than about 150 ~~angstroms~~ Angstroms, more preferably less than about 100 ~~angstroms~~ Angstroms, and most preferably less than about 50 Angstroms, about 40 Angstroms or about 30 Angstroms ~~angstroms~~.

On page 20, please replace paragraph **[0071]** with the following amended paragraph:

**[0071]** The gap between the electrodes can be an air gap, filled with oxygen or with an inert gas (*e.g.* argon, *etc.*), a vacuum, or the gap can be filled with an insulator, semiconductor, or a dielectric. In preferred embodiments, the gap between the electrodes is filled with an insulator. Preferred insulators include~~,~~ elements, compounds or substances that have a resistivity greater than about $10^{-3}$ ohm-meters, preferably greater than about $10^{-2}$ ohm-

meters, more preferably greater than about $10^{-1}$ ohm-meters, and most preferably greater than about 10 ohm meters. Particularly preferred insulators include, but are not limited to, $SiO_2$, $TiO_2$, $ZrO_2$, porcelain, ceramic, glass, clay, polystyrene, TEFLON ~~Teflon~~, plastics having a resistivity greater than $10^{-3}$ ohm-meters, and other high resistivity plastics, insulating oxides or sulfides of the transition metals in the periodic table of elements, and the like.

On page 21, please replace paragraph **[0076]** with the following amended paragraph:

**[0076]** Certain preferred configurations are illustrated in Figures ~~4and~~ 4 and 6A through 6C. Thus, for example, Figure 4B illustrates a flush-faced sensor array. The electrodes and insulators are integrated into a multi-layer material presenting a flush surface. Analyte(s) or solutions containing analytes pass across the surface where the analytes are bound by the binding agent(s) **14.** Figure 6A illustrates an embodiment where the electrodes protrude from the intervening insulator and thereby form one or more channels. The channels are useful for guiding reagents/analytes, and the like, *e.g.* in various microfluidics devices. The binding agent(s) attached to the electrodes form convenient "detector domains" in such channels. Such devices are readily fabricated by providing a multi-layer material, *e.g.* as described below, and selectively etching insulator away from the electrodes.

On page 21, please replace paragraph **[0077]** with the following amended paragraph:

**[0077]** Still another embodiment is illustrated in Figure ~~6C~~ 6B. In this embodiment, insulator/support is removed between the electrodes thereby forming channels within the substrate having electrode walls. Optional biasing electrodes **22** are illustrated in ~~these diagrams~~ Figure 6B.

On page 21, please replace paragraph **[0078]** with the following amended paragraph:

**[0078]** Figure ~~6D~~ 6C illustrates a close channel or well (cross-section) in which sensor element arrays are present in two walls of the channel.

On page 22, please replace paragraph **[0080]** with the following amended paragraph:

**[0080]** Preferred sensor arrays comprise at least two, preferably at least 10, more preferably at least 100, and most preferably at least ~~1, 000~~ 1,000, 10,000, or 1,000,000 sensor

elements. The sensor elements can all bear the same biological molecules **14** or various sensor elements can bear different biological molecules and show specificity for different analytes. Thus, in certain embodiments, a single sensor array can detect/quantify two or more, preferably four or more, more preferably 10 or more, still more preferably 100 or more or 1000 or more, and most preferably 10000 or more, 100,000 or more, or even 1,000,000 or more different analytes. In some molecular sensor apparatus in accordance with the present invention, the molecular sensor apparatus comprises $10^2$ to $10^{10}$ electrode pairs.

On page 35, please replace paragraph **[0129]** with the following amended paragraph:

**[0129]** Such electrode arrays are readily fabricated using sputtering techniques (*see, e.g.* U.S. Patents 5,203,977, 5,486,277, ~~RE37,032,~~ 5,742,471, and the like). Sputtering is a vacuum coating process where an electrically isolated cathode is mounted in a chamber that can be evacuated and partially filled with an inert gas. If the cathode material is an electrical conductor, a direct-current high-voltage power supply is used to apply the high voltage potential. If the cathode is an electrical insulator, the polarity of the electrodes is reversed at very high frequencies to prevent the formation of a positive charge on the cathode that would stop the ion bombardment process. Since the electrode polarity is reversed at a radio frequency, this process is referred to as RF-sputtering.

On page 35, please replace paragraph **[0130]** with the following amended paragraph:

**[0130]** Magnetron sputtering is a more effective form than diode sputtering that uses a magnetic field to trap electrons in a region near the target surface creating a higher probability of ionizing a gas atom. The high density of ions created near the target surface causes material to be removed many times faster than in diode sputtering. The magnetron effect is created by an array of permanent magnets included within the cathode assembly that produce a magnetic field normal to the electric field. While other sputtering techniques may be used, in particularly preferred embodiments, magnetron sputtering, *e.g.* as described in U.S. Patent 5,486,277, s is used to provide the electrode arrays of this invention.

On page 35, please replace paragraph **[0131]** with the following amended paragraph:

**[0131]** The binding agents (*e.g.* biomolecules) are attached to the electrodes using methods well known to those of skill in the art. Typically the electrode(s) and/or the ~~bindign~~

binding agent(s) are derivatized (functionalized) with reactive moieties (*e.g.* linkers) that facilitate attachment of the electrode to the binding agent. Thus, for example in certain embodiments, the binding agent bears a reactive linker (*e.g.* an aliphatic thiol linker) that reacts with the electrode surface or with a functional group attached thereto, and/or the electrode is derivatized with a linker that binds to the biomolecule.

On page 38, please replace paragraph **[0143]** with the following amended paragraph:

**[0143]** This approach is simply illustrative. Numerous other ~~approached~~ approaches can be used to attach the biological molecule to the respective electrode(s). Such approaches include, but are not limited to attachment of chemical groups to the surface through the use of photoactivatable chemistries (*see, e.g.,* Sundberg *et al.* (1995) *J. Am. Chem. Soc.* 117(49):12050-12057), micro-stamping techniques (*see, e.g.,* Kumar *et al.* (1994) *Langmuir* 10(5):1498-1511; Kumar *et al.* (1993) *Appl. Phys. Lett.* 63(14):2002-2004), and the like.

On page 50, please replace paragraph **[0200]** with the following amended paragraph:

**[0200]** The electrodes are dried again under nitrogen or argon. A voltage (4-7 volts) is applied again to the electrodes and the current is measured. ~~again to macro electrodes and measure the current.~~ The measured current of the hybridized nucleic acids is significantly greater than the current measured for the unhybridized electrodes.

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. (Currently Amended) A molecular sensing apparatus comprising:

one or more electrode pairs, wherein at least one electrode pair in said one or more electrode pairs comprises:

a first electrode;

a second electrode; and

an insulator between said first electrode and said second electrode, wherein a portion of said insulator is removed between said first electrode and said second electrode thereby forming a channel within said insulator; and

wherein said first electrode and said second electrode are separated by a distance that would allow a biological macromolecule or biological macromolecule/analyte complex to connect ~~connecting~~ said first electrode to said second electrode.

2-4. (Canceled)

5. (Currently Amended) The molecular sensing apparatus of claim 1, wherein said insulator has a resistivity greater than $10^{-3}$ ohm-meters.

6. (Currently Amended) The molecular sensing apparatus of claim ~~5~~ 1, wherein said insulator is selected from the group consisting of $SiO_2$, $TiO_2$, $ZrO_2$, quartz, porcelain, ceramic, polystyrene, ~~teflon~~ TEFLON, and an insulating oxide or sulfide of a transition metal in the periodic table of the elements.

7. (Currently amended) The molecular sensing apparatus of claim 1, wherein said first electrode and said second electrode are separated by a distance in the range of 1 Angstrom to $10^{10}$ Angstroms.

8. (Currently amended) The molecular sensing apparatus of claim 1, wherein said first electrode and said second electrode are separated by a distance less than ~~about~~ 70 Angstroms.

9. (Currently amended) The molecular sensing apparatus of claim 1, wherein at least one of

said first electrode and said second electrode has a resistivity of less than $10^{-2}$ ohm-meters.

10. (Currently amended) The molecular sensing apparatus of claim 1, wherein at least one of said first electrode and said second electrode has a resistivity of less than $10^{-3}$ ohm-meters.

11. (Currently amended) The molecular sensing apparatus of claim 1 ~~9~~, wherein said first electrode and said second electrode ~~the electrodes comprise~~ each comprises a material selected from the group consisting of ruthenium, osmium, cobalt, rhodium, rubidium, lithium, sodium, potassium, vanadium, cesium, beryllium, magnesium, calcium, chromium, molybdenum, silicon, germanium, aluminum, iridium, nickel, palladium, platinum, iron, copper, titanium, tungsten, silver, gold, zinc, cadmium, indium tin oxide, carbon, and ~~a~~ carbon nanotube.

12. (Currently amended) The molecular sensing apparatus of claim 1, wherein at least one of said first electrode and said second electrode is functionalized ~~to contain~~ with a chemical group that can be derivatized or crosslinked.

13. (Currently amended) The molecular sensing apparatus of ~~claim 12~~ claim 12, wherein ~~the~~ said chemical group is selected from the group consisting of a sulfate, a sulfhydryl, an amine, an aldehyde, a carboxylic acid, a phosphate, a phosphonate, an alkene, an alkyne, a hydroxyl ~~group~~, a bromine, an iodine, a chlorine, a light-activatable group, and a group activatable by an electric potential.

14. (Currently amended) The molecular sensing apparatus of claim 1, wherein at least one of said first electrode and said second electrode bears a self-assembled monolayer (SAM).

15. (Currently amended) The molecular sensing apparatus of claim 14, wherein said SAM comprises a compound selected from the group consisting of an alkanethiol, a phospholipid, a bola amphiphile, and an oligo(phenylenevinylene). ~~1~~

16-19. (Canceled)

20. (Currently amended) The molecular sensing apparatus of claim 1, further comprising a substrate that supports ~~to support~~ the first electrode and the second electrode, wherein the first electrode and the second electrode are integrated with the substrate.

21. (Currently amended) The molecular sensing apparatus of claim 1~~, further comprising a substrate with the first electrode and the second electrode,~~ wherein the first electrode and the second electrode are integrated with the insulator to form a substrate.

22. (Currently amended) The molecular sensing apparatus of claim 1,~~,~~ wherein said first electrode comprises a surface with a shape selected from the group consisting of convex, concave, textured, corrugated, patterned uniformly, and randomly patterned.

23. (Currently amended) The molecular sensing apparatus of claim 1,~~,~~ wherein said first electrode and said second electrode are oriented in a formation selected from the group consisting of annular, planar, and orthogonal.

24. (Currently Amended) The molecular sensing apparatus of claim 1, wherein the first electrode ~~comprises~~ has a first surface and ~~a~~ said second electrode ~~comprises~~ has a second surface, wherein the first surface is not coplanar to ~~and~~ the second surface ~~are not co-planar~~.

25. (Currently amended) The apparatus of claim 1, wherein said as least one electrode pair comprises a first electrode pair and a second electrode pair ~~the first electrode and the second electrode comprise a first electrode pair, the molecular sensing apparatus further comprising a second electrode pair comprising a second first electrode and a second second electrode~~.

26. (Currently amended) The molecular sensing apparatus of claim ~~25~~ 1, wherein said ~~apparatus comprises~~ one or more electrode pairs are at least ~~20~~ 10 electrode pairs.

27. (Currently amended) The molecular sensing apparatus of claim ~~25~~ 1, wherein said ~~apparatus comprises~~ one or more electrode pairs are at least ~~100~~ 1,000 electrode pairs.

28. (Currently amended) The molecular sensing apparatus of claim ~~25~~ 1, wherein said ~~apparatus~~ one or more electrode pairs comprises ~~about~~ $10^2$ to $10^{10}$ electrode pairs.

29. (Currently amended) The molecular sensing apparatus of claim ~~25~~ 1, the molecular sensing apparatus further comprising a measurement device electrically coupled to ~~the~~ each first electrode and to ~~the~~ each second electrode of each electrode pair in said at least one electrode pair.

30. (Currently amended) The molecular sensing apparatus of claim 29, wherein said measurement device measures an electromagnetic property selected from the group consisting of direct electric current, alternating electric current, permitivity, resistivity, electron transfer, electron tunneling, electron hopping, electron transport, electron conductance, voltage, electrical impedance, signal loss, dissipation factor, resistance, capacitance, inductance, magnetic field, electrical potential, charge and magnetic potential.

31. (Currently amended) The molecular sensing apparatus of claim 1, further comprising an electrical circuit electrically coupled to the first electrode and the second electrode.

32. (Currently amended) The molecular sensing apparatus of claim 31, wherein said electrical circuit comprises an ~~electrical~~ electric signal gating system.

33. (Currently amended) The molecular sensing apparatus of claim 32, wherein ~~the~~ said electric signal gating system comprises a CMOS gating system.

34. (Currently amended) The apparatus of claim 25, wherein

a first biological macromolecule is attached to the first electrode and the second electrode in the first electrode pair, and

a second biological macromolecule is attached to the first electrode and the second electrode in the second electrode pair; wherein the first biological molecule and the second biological molecule are the same ~~the electrodes comprising the first and second electrode pairs have attached the same biological macromolecule~~.

35. (Currently amended) The apparatus of claim 25, wherein

a first biological macromolecule is attached to the first electrode and the second electrode in the first electrode pair, and

a second biological macromolecule is attached to the first electrode and the second electrode in the second electrode pair; wherein the first biological molecule and the second biological molecule are different ~~the electrodes comprising the first and second electrode pairs have attached different biological molecules~~.

36. (Currently amended) The molecular sensing apparatus of claim 1, further comprising a computer electrically coupled to the first electrode and the second electrode ~~of at least one electrode pair~~.

37. (Currently amended) The molecular sensing apparatus of claim 1, wherein at least one of the first electrode and the second electrode comprises a ~~semi-conducting~~ semiconductor material.

38. (Currently amended) The molecular sensing apparatus of claim 37, wherein said ~~semi-conducting~~ semiconductor material has a resistivity ranging from ~~about~~ $10^{-6}$ Ω-m to ~~about~~ $10^{7}$ Ω-m.

39. (Currently amended) The molecular sensing apparatus of claim 37, wherein the ~~semi-conducting~~ semiconductor material is selected from the group consisting of silicon, dense silicon carbide, boron carbide, $Fe_3O_4$, germanium, silicon germanium, ~~silcon~~ silicon carbide, tungsten carbide, titanium carbide, indium phosphide, gallium nitride, gallium phosphide, aluminum phosphide, aluminum arsenide, mercury cadmium telluride, tellurium, selenium, ZnS, ZnO, ZnSe, CdS, ZnTe, GaSe, CdSe, CdTe, GaAs, InP, GaSb, EnAs, Te, PbS, InSb, PbTe, PbSe, and tungsten disulfide.

40. (Canceled)

41. (Original) A method of making a molecular sensing apparatus, said method comprising:

providing a first electrode and a second electrode separated by an insulator;

contacting said first and said second electrode with a first solution comprising a biological macromolecule;

placing a charge on said first electrode to attract said biological macromolecule to said first electrode where said macromolecule attaches to said first electrode to form an attached macromolecule; and

placing a charge on said second electrode to attract a portion of said attached macromolecule to said second electrode where said macromolecule attaches to said second electrode.

42. (Original) The method of 41, wherein said biological macromolecule is selected from the group consisting of a nucleic acid, a proteins, a polysaccharide, a lectin, and a lipid.

43. (Original) The method of claim 41, wherein said biological macromolecule is functionalized with a chemical group selected from the group consisting of a sulfate, a sulfhydryl, an amine, an aldehyde, a carboxylic acid, a phosphate, a phosphonate, an alkene,

an alkyne, a hydroxyl group, a bromine, an iodine, a chlorine, a light-activatable group, and a group activatable by an electric potential.

44. (Original) The method of claim 41, wherein said biological macromolecule is selected from the group consisting of a nucleic acid, a protein, a polysaccharide, a lectin and a lipid.

45. (Original) The method of claim 41, wherein said biological macromolecule is a nucleic acid.

46. (Original) The method of claim 41, wherein said insulator has a resistivity of greater than about $10^{-3}$ Ω-m.

47. (Original) The method of claim 41, wherein said insulator is selected from the group containing $SiO_2$, $TiO_2$, $ZrO_2$, porcelain, ceramic, quartz, high resistivity plastic, and an insulating oxide or sulfide of the transition metals in the periodic table of the elements.

48. (Original) The method of 41, wherein said first electrode and said second electrode are separated by a distance range from about 1 to about $10^{10}$ Angstroms.

49. (Original) The method of claim 41, wherein said first electrode and said second electrode are separated by a distance less than about 70 Angstroms.

50. (Original) The method of claim 41, wherein said first electrode and said second electrode have a resistivity of less than about $10^{-3}$ Ω-m.

51. (Original) The method of claim 41, wherein said first electrode and said second electrode comprise a material selected from the group consisting of ruthenium, osmium, cobalt, rhodium, rubidium, lithium, sodium, potassium, vanadium, cesium, beryllium, magnesium, calcium, chromium, molybdenum, silicon, germanium, aluminum, iridium, nickel, palladium, platinum, iron, copper, titanium, tungsten, silver, gold, zinc, cadmium, indium tin oxide, carbon, and a carbon nanotube.

52. (Original) The method of claim 41, wherein said first electrode is functionalized to bear a chemical group capable of being further derivatized or crosslinked.

53. (Original) The method of claim 52, wherein the said chemical group is selected from the group consisting of functionalized with a chemical group selected from a sulfate, a sulfhydryl, an amine, an aldehyde, a carboxylic acid, a phosphate, a phosphonate, an alkene, an alkyne, a hydroxyl group, a bromine, an iodine, a chlorine, a light-activatable group, a group activatable by an electric potential.

54. (Original) The method of claim 41, wherein said biological macromolecule is attached to said first electrode by an electrically conductive linker.

55. (Original) The method of claim 54, wherein said linker is selected from the group consisting of DFDNB, DST, ABH, ANB-NOS, EDC, NHS-ASA, and SIA.

56. (Original) The method of claim 54, wherein said linker is oligo(phenylenevinlyene).

57. (Original) The method of claim 41, further comprising a substrate to support the first electrode and the second electrode, wherein the first electrode and the second electrode are integrated with the substrate.

58. (Original) The method of claim 41, further comprising a substrate with the first electrode and the second electrode, wherein the first electrode and the second electrode are integrated with the insulator to form a substrate.

59. (Original) The method of claim 41, wherein the first electrode and the second electrode provide a first electrode pair, the molecular sensing apparatus further comprising a second electrode pair comprising a second first electrode and a second second electrode.

60. (Original) The method of claim 59, wherein said apparatus comprises at least 3 electrode pairs.

61. (Original) The method of claim 59, wherein said apparatus comprises at least 100 electrode pairs.

62. (Original) The method of claim 59, wherein said apparatus comprises about $10^2$ to about $10^{10}$ electrode pairs.

63. (Original) The method of claim 59, further comprising:

contacting said second electrode pair with a second solution comprising a second biological macromolecule;

placing a charge on a first electrode of said second electrode pair to attract said second biological macromolecule to said first electrode of said second electrode pair whereby said second biological macromolecule attaches to said first electrode to form an attached second macromolecule; and

placing a charge on said second electrode of said second electrode pair to attract a portion of said attached second macromolecule to said second electrode whereby said second macromolecule attaches to said second electrode of said second electrode pair.

64. (Original) The method of claim 63, wherein said apparatus comprises a third electrode pair.

65. (Original) The method of claim 63, wherein said apparatus comprises greater than 3 electrode pairs.

66. (Original) The method of claim 63, wherein said first solution and said second solution are the same.

67. (Original) The method of claim 63, wherein said first solution and said second solution are different.

68. (Original) The method of claim 63, wherein said first biological molecule and said second biological molecule are the same.

69. (Original) The method of claim 63, wherein said first biological molecule and said second biological molecule are the different.

70. (Original) The method of claim 41, wherein at least one of said first electrode and said second electrode comprise a semi-conducting material.

71. (Original) The method of claim 70, wherein the semi-conductor material has a resistivity in the range of $10^{-6}$ Ω-m to $10^{-7}$ Ω-m.

72. (Original) The method of claim 70, wherein the semi-conducting material is selected from the group consisting of silicon, dense silicon carbide, boron carbide, $Fe_3O_4$, germanium,

siliconj germanium, silcon carbide, tungsten carbide, titanium carbide, indium phosphide, gallium nitride, gallium phosphide, aluminum phosphide, aluminum arsenide, mercury cadmium telluride, tellurium, selenium, ZnS, ZnO, ZnSe, CdS, ZnTe, GaSe, CdSe, CdTe, GaAs, InP, GaSb, InAs, Te, PbS, InSb, PbTe, PbSe, and tungsten disulfide.

73. (Original) A method of detecting an analyte said method comprising:

i) providing molecular sensing apparatus comprising a first electrode and a second electrode separated by an insulator where said first electrode has a biological macromolecule attached thereto;

ii) contacting the attached macromolecule with said analyte whereby said analyte binds to said macromolecule thereby forming a macromolecule/analyte complex;

iii) placing a charge on said second electrode attract a portion of said bound analyte to said second electrode where said analyte is bound to said second electrode such that said macromolecule/analyte complex forms a connection between said first electrode and said second electrode; and

iv) detecting the connection between said first and said second electrode.

74. (Original) The method of claim 73, wherein said providing comprises:

contacting said first electrode with a first solution comprising said biological macromolecule; and

placing a charge on said first electrode whereby said charge attracts said biological macromolecule to said electrode and said biological macromolecule attaches to said electrode.

75. (Original) The method of claim 73, wherein said placing a charge, further comprising placing a charge on said first electrode opposite to the charge on said second electrode.

76. (Original) The method of claim 73, wherein said detecting comprises detecting an electromagnetic property selected from the group consisting of direct electric current, alternating electric current, permittivity, resistivity, electron transfer, electron tunneling, electron hopping, electron transport, electron conductance, voltage, electrical impedance, signal loss, dissipation factor, resistance, capacitance, inductance, magnetic field, electrical potential, charge, and magnetic potential.

77. (Original) The method of claim 73, wherein said biological macromolecule is selected from the group consisting of a nucleic acid, a protein, a polysaccharide, a lectin, and a lipid.

78. (Original) The method of claim 78, wherein said biological macromolecule is a nucleic acid.

79. (Original) The method of claim 78, wherein said biological macromolecule is functionalized with a chemical group selected from the group consisting of a sulfate, a sulfhydryl, an amine, an aldehyde, a carboxylic acid, a phosphate, a phosphonate, an alkene, an alkyne, a hydroxyl group, a bromine, an iodine, a chlorine, a light-activatable group, and a group activatable by an electric potential.

80. (Original) The method of claim 73, wherein said insulator has a resistivity greater than $10^{-3}$ Ω-m.

81. (Original) The method of claim 73, wherein said insulator is selected from the group consisting of $SiO_2$, $TiO_2$, $ZrO_2$, porcelain, ceramic, a high resistivity plastic, and an insulating oxide or sulfide of a transition metal in the periodic table of the elements.

82. (Original) The method of claim 73, wherein said first electrode and said second electrode are separated by a distance less than about 70 Angstroms.

83. (Original) The method of claim 73, wherein said first electrode and said second electrode are separated by a distance ranging from about 1 to about $10^{10}$ Angstroms.

84. (Original) The method of claim 73, wherein said first electrode and said second electrode have a resistivity of less than about $10^{-2}$ Ω-m.

85. (Original) The method of claim 73, wherein said first electrode comprises a semi-conductor material.

86. (Original) The method of claim 88, wherein said semi-conductor material having has a resistivity ranging from about $10^{-6}$ Ω-m to about $10^{-7}$ Ω-m.

87. (Original) The method of claim 88, wherein the semi-conducting material is selected from the group consisting of silicon, dense silicon carbide, boron carbide, $Fe_3O_4$, germanium, silicon germanium, silcon carbide, tungsten carbide, titanium carbide, indium phosphide, gallium nitride, gallium phosphide, aluminum phosphide, aluminum arsenide, mercury

cadmium telluride, tellurium, selenium, ZnS, ZnO, ZnSe, CdS, ZnTe, GaSe, CdSe, CdTe, GaAs, InP, GaSb, InAs, Te, PbS, InSb, PbTe, PbSe, and tungsten disulfide.

88. (Original) The method of claim 73, wherein said first electrode and said second electrode are formed from a material selected from the group consisting of ruthenium, osmium, cobalt, rhodium, rubidium, lithium, sodium, potassium, vanadium, cesium, beryllium, magnesium, calcium, chromium, molybdenum, silicon, germanium, aluminum, iridium, nickel, palladium, platinum, iron, copper, titanium, tungsten, silver, gold, zinc, cadmium, indium tin oxide, carbon, and a carbon nanotube.

89. (Original) The method of 73, wherein at 1 said first electrode is functionalized to bear a chemical group capable of being further derivatized or crosslinked.

90. (Original) The method of claim 89, wherein the said chemical group is selected from the group consisting of a sulfate, a sulfhydryl, an amine, an aldehyde, a carboxylic acid, a phosphate, a phosphonate, an alkene, an alkyne, a hydroxyl group, a bromine, an iodine, a chlorine, a light-activatable group, and a group activatable by an electric potential.

91. (Original) The method of claim 89, wherein said functionalized biological macromolecule is attached to said first electrode by an electrically conductive linker.

92. (Original) The method of claim 91, wherein said linker is selected from the group consisting DFDNB, DST, ABH, ANB-NOS, EDC, NHS-ASA, and SIA.

93. (Original) The method of claim 91, wherein said linker is oligo(phenylenevinylene).

94. (Original) The method of claim 73, wherein the first electrode and the second electrode are integrated with a substrate.

95. (Original) The method of claim 73, wherein the first electrode and the second electrode are integrated with the insulator to form a substrate.

96. (Original) The method of claim 73, wherein the first electrode and the second electrode provide a first electrode pair, the molecular sensing apparatus further comprising a second electrode pair comprising a second first electrode and a second electrode.

97. (Original) The method of claim 96, wherein said apparatus comprises at least 3 electrode pairs.

98. (Original) The method of claim 96, wherein said apparatus comprises at least 100 electrode pairs.

99. (Original) The method of claim 96, wherein said apparatus comprises from about $10^2$ to about $10^{10}$ electrode pairs.

100. (Original) The method of claim 96, further comprising performing steps ii, iii, and iv with said second electrode pair

d) contacting the second biological macromolecule with said sample potentially comprising said analyte so that any analyte in said sample binds to said second biological macromolecule thereby forming a second biological macromolecule/analyte complex;

e) placing a charge on said fourth electrode to attract a portion of any said second biological macromolecule/analyte complex to said fourth electrode thereby forming a connection between said third electrode and said fourth electrode; and

f) detecting any said connection between the third electrode and the fourth electrode.

101. (Original) The method of claim 96, wherein the biological macromolecule on said first electrode pair is different than the biological macromolecule attached to the second electrode pair.

102. (Original) A method of detecting an analyte, said method comprising:

i) providing a molecular sensing apparatus comprising a first electrode and a second electrode separated by a spacer where said first electrode has a first biological macromolecule attached thereto and said second electrode has a second biological macromolecule attached thereto;

ii) contacting the first attached macromolecule and the a second attached macromolecule with said analyte whereby said analyte binds to the first macromolecule and to the second macromolecule thereby forming a macromolecule/analyte complex forming a connection between said first electrode and said second electrode; and

iii) detecting the connection between said first and said second electrode.

103. (Original) The method of 102, wherein said providing comprises:

contacting said first electrode with a first solution comprising said first biological macromolecule; and

placing a charge on said first electrode whereby said charge attracts said first biological macromolecule to said electrode and said biological macromolecule attaches to said electrode.

104. (Original) The method of claim 102, wherein said detecting comprises detecting an electromagnetic property selected from the group consisting of direct electric current, alternating electric current, permitivity, resistivity, electron transfer, electron tunneling, electron hopping, electron transport, electron conductance, voltage, electrical impedance, signal loss, dissipation factor, resistance, capacitance, inductance, magnetic field, electrical potential, charge and magnetic potential.

105. (Original) The method of claim 102, wherein said biological macromolecule is selected from the group consisting of a nucleic acid, a protein, a polysaccharide, a lectin, and a lipid.

106. (Original) The method of claim 102, wherein said biological macromolecule is a nucleic acid.

107. (Original) The method of claim 106, wherein said biological macromolecule is functionalized with a chemical group selected from the group consisting of a sulfate, a sulfhydryl, an amine, an aldehyde, a carboxylic acid, a phosphate, a phosphonate, an alkene, an alkyne, a hydroxyl group, a bromine, an iodine, a chlorine, a light-activatable group, and a group activatable by an electric potential.

108. (Original) The method of claim 102, wherein said insulator has a resistivity greater than $10^{-3}$ Ω-m.

109. (Original) The method of claim 102, wherein said insulator is selected from the group consisting of $SiO_2$, $TiO_2$, $ZrO_2$, ceramic, porcelain, a high resistivity plastic, and an insulating oxide or sulfide of a transition metal in the periodic table of the elements.

110. (Original) The method of claim 102, wherein said first electrode and said second electrode are separated by a distance less than about 70 Angstroms.

111. (Original) The method of claim 102, wherein said first electrode and said second electrode are separated by a distance ranging from about 1 to about $10^{10}$ Angstroms.

112. (Original) The method of claim 102, wherein said first electrode and said second electrode have a resistivity of less than about $10^{-2}$ Ω-m.

113. (Original) The method of claim 102, wherein said first electrode and said second electrode comprise a material selected from the group consisting of ruthenium, osmium, cobalt, rhodium, rubidium, lithium, sodium, potassium, vanadium, cesium, beryllium, magnesium, calcium, chromium, molybdenum, silicon, germanium, aluminum, indium, nickel, palladium, platinum, iron, copper, titanium, tungsten, silver, gold, zinc, cadmium, indium tin oxide, carbon, and a carbon nanotube.

114. (Original) The method of claim 102, wherein at least one of the first electrode and the second electrode comprises a semi-conductor material.

115. (Original) The method of claim 114, wherein said semi-conductor material has a resistivity ranging from about $10^{-3}$ Ω-cm to about $10^{-7}$ Ω-cm.

116. (Original) The method of claim 114, wherein said semi-conducting material is selected from the group consisting of silicon, dense silicon carbide, boron carbide, $Fe_3O_4$, germanium, silicon germanium, silcon carbide, tungsten carbide, titanium carbide, indium phosphide, gallium nitride, gallium phosphide, aluminum phosphide, aluminum arsenide, mercury cadmium telluride, tellurium, selenium, ZnS, ZnO, ZnSe, CdS, ZnTe, GaSe, CdSe, CdTe, GaAs, InP, GaSb, InAs, Te, PbS, InSb, PbTe, PbSe, and tungsten disulfide.

117. (Original) The method of claim 102, wherein said first electrode and said second electrode are formed from a material selected from the group consisting of ruthenium, osmium, cobalt, rhodium, aluminum, iridium, nickel, palladium, platinum, iron, copper, titanium, tungsten, silver, gold, zinc, cadmium, indium tin oxide, carbon, and a carbon nanotube.

118. (Original) The method of claim 102, wherein at least one of the said first electrode and second electrode is functionalized to contain a chemical group capable of being further derivatized or crosslinked.

119. (Original) The method of claim 118, wherein the said chemical group is selected from the group consisting of an a sulfate, a sulfhydryl, an amine, an aldehyde, a carboxylic acid, a phosphate, a phosphonate, an alkene, an alkyne, a hydroxyl group, a bromine, an iodine, a chlorine, a light-activatable group, and a group activatable by an electric potential.

120. (Original) The method of claim 118, wherein said functionalized biological macromolecule is attached to said first electrode by an electrically conductive linker.

121. (Original) The method of claim 120, wherein said linker is selected from the group consisting DFDNB, DST, ABH, ANB-NOS, EDC, NHS-ASA, and SIA.

122. (Original) The method of claim 120, wherein said linker is oligo(phenylenevinylene).

123. (Original) The method of claim 102, wherein the first electrode and the second electrode are integrated with a substrate.

124. (Original) The method of claim 102, wherein the first electrode and the second electrode are integrated with the insulator to form a substrate.

125. (Original) The method of claim 102, wherein the first electrode and the second electrode provide a first electrode pair, the molecular sensing apparatus further comprising a second electrode pair comprising a second first electrode and a second electrode.

126. (Original) The method of claim 125, wherein said apparatus comprises at least 3 electrode pairs.

127. (Original) The method of claim 125, wherein said apparatus comprises at least 100 electrode pairs.

128. (Original) The method of claim 132, wherein said apparatus comprises from about $10^2$ to about $10^{10}$ electrode pairs.

129. (Original) The method of claim 125, further comprising: performing steps ii and iii with said second electrode pair

c) contacting the analyte with the third biological macromolecule and the fourth biological macromolecule thereby forming a second macromolecule/analyte complex

comprising the third biological macromolecule, the fourth biological macromolecule and the analyte, wherein the macromolecule/analyte complex connects said first electrode and said second electrode in said second electrode pair; and

d) detecting the connection between said first electrode and said second electrode in said second electrode pair.

130. (Original) The method of claim 125, wherein at least one of the biological macromolecule on an electrode of the second pair is different from either of the biological macromolecules on the electrodes of the first electrode pair.

131. (Original) The method of claim 125, wherein the biological on the electrode of the second electrode pair are different from the biological macromolecules on the electrodes of the first electrode pair.

132. (Original) A method of detecting an analyte, said method comprising:

i) providing a molecular sensing apparatus comprising a first electrode and a second electrode separated by a spacer where a biological macromolecule forms a connection between said first electrode and said second electrode;

ii) detecting the connection between said first and said second electrode;

iii) contacting the attached macromolecule with said analyte whereby said analyte binds to said macromolecule forming a macromolecule/analyte complex; and

iv) detecting the difference in the connection between said first electrode and said second electrode.

133. (Original) The method of claim 132, wherein said contacting comprises placing a charge on said first electrode whereby said charge attracts said analyte to said biological macromolecule.

134. (Original) The method of claim 132, wherein said providing comprises

contacting said first electrode with a first solution comprising said biological macromolecule; and

placing a charge on said first electrode whereby said charge attracts said biological macromolecule to said electrode and said biological macromolecule attaches to said electrode and

placing a charge on said second electrode to attract a portion of said bound macromolecule to said second electrode where said macromolecule is bound to said second

electrode such that said macromolecule forms a connection between said first electrode and said second electrode.

135. (Original) The method of claim 132, wherein said placing a charge comprises placing a charge on said first electrode opposite to the charge on said second electrode.

136. (Original) The method of claim 132, wherein said detecting comprises detecting an electromagnetic property selected from the group consisting of direct electric current, alternating electric current, permittivity, resistivity, electron transfer, electron tunneling, electron hopping, electron transport, electron conductance, voltage, electrical impedance, signal loss, dissipation factor, resistance, capacitance, inductance, magnetic field, electrical potential, charge and magnetic potential.

137. (Original) The method of claim 132, wherein said biological macromolecule is selected from the group consisting of a nucleic acid, a protein, a polysaccharide, a lectin or a lipid.

138. (Original) The method of claim 132, wherein said biological macromolecule is a nucleic acid.

139. (Original) The method of claim 132, wherein said analyte is a protein or protein complex.

140. (Original) The method of claim 132, wherein said biological macromolecule is functionalized with a chemical group consisting of a sulfhydryl, an amine, an aldehyde, a carboxylic acid, a phosphate, a phosphonate, an alkene, an alkyne, a hydroxyl, bromine, iodine, chlorine, a chemical group that can be activated by light, and a chemical group that can be activated by the application of an electrical potential.

141. (Original) The method of claim 132, wherein said insulator is selected from the group consisting of elements, compounds or substances that have resistivities greater than $10^{-3}$ Ω-m.

142. (Original) The method of claim 141, wherein said insulator is selected from the group containing $SiO_2$, $TiO_2$, $ZrO_2$, porcelain, polystryene, polystyrene, organic compounds produced by polymerization having a resistivity greater than $10^{-3}$ Ω-m, and insulating oxides or sulfides of the transition metals in the periodic table of the elements.

143. (Original) The method of claim 132, wherein said first electrode and said second electrode are separated by a distance less than about 70 Angstroms.

144. (Original) The method of claim 132, wherein said first electrode and said second electrode are separated by a distance in the range of 1 to $10^9$ Angstroms.

145. (Original) The method of claim 132, wherein at least one said first electrode and said second electrode are formed of a material selected from the group consisting of elements, compounds or substances that have resistivities of less than $10^{-2}$ Ω-m.

146. (Original) The method of claim 145, wherein the said first electrode and said second electrode are formed from a material selected from the group consisting of , ruthenium, osmium, cobalt, rhodium, rubidium, lithium, sodium, potassium, vanadium, cesium, beryllium, magnesium, calcium, chromium, molybdenum, silicon, germanium, aluminum, iridium, nickel, palladium, platinum, iron, copper, titanium, tungsten, silver, gold, zinc, cadmium, indium tin oxide, carbon or carbon nanotubes or alloys or compounds of these materials.

147. (Original) The method of claim 132, wherein at least one of the first electrode and the second electrode comprises a semiconductor material.

148. (Original) The method of claim 132, wherein said semi-conductor material has a resistivity ranging from about $10^{-2}$ Ω-m to about $10^9$ Ω-m.

149. (Original) The method of claim 148, wherein the semi-conducting material is selected from the group consisting of silicon, dense silicon carbide, boron carbide, $Fe_3O_4$, germanum, silicon germanium, silicon carbide, tungsten carbide, titanium carbide, indium phosphide, gallium nitride, gallium phosphide, aluminum phosphide, aluminum arsenide, mercury cadmium telluride, tellurium, selenium, tungsten disulfide, ZnS, ZnO, ZnSe, CdS, ZnTe, GaSe, CdSe, CdTe, GaAs, InP, GaSb, InAs, PbS, InSb, PbTe, and PbSe.

150. (Original) The method of claim 132, wherein at least one of said first electrode and second electrode is functionalized to contain a chemical group capable of being further derivatized or crosslinked.

151. (Original) The method of claim 132, wherein said chemical group is selected from the group consisting of a sulfhydryl, an amine, an aldehyde, a carboxylic acid, a phosphate, an alkene, an alkyne, a hydroxyl group, bromine, iodine, chlorine, a chemical group that can be activated by light of wavelength ranging from 190 nm to 700 nm, a flourinated aryl azide, a benzophenone, (R,S)-1-(3,4- (methylene-dioxy)-6-nitrophenyl) ethyl cholorformate [-] (MeNPOC), N-((2-pyridyl, ethyl)-4-azido) salicylamide or a chemical group that can be activated by the application of an electrical potential , such as S-benzyloxycarbonyl derivatives, S-benzyl thioethers, S-phenyl thioethers, S-4-picolyl thioethers, S-2,2,2-trichloroethoxycarbonyl derivatives, S-triphenylmethyl thioethers.

152. (Original) The method of claim 132, wherein said biological macromolecule is attached to said first electrode by an electrically conductive linker.

153. (Original) The method of claim 132, wherein said linker is selected from the group consisting of chemical crosslinkers capable of linking functional groups, such as DFDNB, DST, ABH, ANB-NOS, EDC, NHS, NHS-ASA, SIA.

154. (Original) The method of claim 132, wherein said linker is an oligo(phenylenevinylene).

155. (Original) The method of claim 132, wherein said apparatus further comprises substrate to support the first electrode and the second electrode, wherein the first electrode and the second electrode are integrated with the substrate.

156. (Original) The method of claim 132, wherein said apparatus further comprises a substrate in which the first electrode and the second electrode are integrated with the insulator to form the substrate.

157. (Original) The method of claim 132, wherein the first electrode and the second electrode provide a first electrode pair, the molecular sensing apparatus further comprising a second electrode pair comprising a second first electrode and a second second electrode.

158. (Original) The method of claim 157, wherein said apparatus comprises at least 3 electrode pairs.

159. (Original) The method of claim 157, wherein said apparatus comprises at least 100 electrode pairs.

160. (Original) The method of claim 157, wherein said apparatus comprises from about in the range of $10^2$ to $10^{10}$ electrode pairs.

161. (Original) The method of claim 157, further comprising: performing steps ii, iii and iv with the second electrode pair

d) detecting an electrical connection between the first electrode and the second electrode in the second electrode pair;

e) contacting the second biological macromolecule that is connected to said first electrode and said second electrode in said second electrode pair with a second analyte whereby said second analyte binds to said second biological macromolecule thereby forming a second macromolecule/analyte complex comprising said second biological macromolecule and said second analyte; and

f) detecting a difference in the electrical connections between said first electrode and said second electrode in said second electrode pair.

162. (Original) The method of claim 157, wherein the biological macromolecule attached to said first electrode pair is the same as the biological macromolecule attached to said second electrode pair.

163. (Original) The method of claim 157, wherein the biological macromolecule attached to said first electrode pair is different from the biological macromolecule attached to said second electrode pair.

164. (Original) The method of claim 157, wherein the analyte attached to said first electrode pair is the same as the analyte attached to said second electrode pair.

165. (Original) The method of claim 157, wherein the analyte attached to said first electrode pair is different from the analyte attached to said second electrode pair.

166. (New) A molecular sensing apparatus comprising one or more electrode pairs in a substrate, wherein a first electrode pair in said one or more electrode pairs comprises a first electrode and a second electrode, wherein a portion of the substrate is removed between said first electrode and said second electrode thereby forming a channel within said substrate with walls formed by said first electrode and said second electrode in said first electrode pair.

167. (New) The molecular sensing apparatus of claim 166 wherein said first electrode and said second electrode in said first electrode pair are separated by a distance that would allow a biological macromolecule to connect said first electrode and said second electrode.

168. (New) The molecular sensing apparatus of claim 166 wherein a biological macromolecule connects said first electrode and said second electrode.

169. (New) The molecular sensing apparatus of claim 168 wherein said biological macromolecule is a nucleic acid.

170. (New) The molecular sensing apparatus of claim 169 wherein said nucleic acid is a deoxyribonucleic acid or a ribonucleic acid.

171. (New) The molecular sensing apparatus of claim 167 wherein said distance is in the range of 1 Angstrom to $10^{10}$ Angstroms.

172. (New) The molecular sensing apparatus of 167 wherein said distance is less than 300 Angstroms.

173. (New) The molecular sensing apparatus of claim 166 wherein at least one of said first electrode and said second electrode has a resistivity of less than $10^{-3}$ ohm-meters.

174. (New) The molecular sensing apparatus of claim 166 wherein said first electrode and said second electrode comprise a material selected from the group consisting of ruthenium, osmium, cobalt, rhodium, rubidium, lithium, sodium, potassium, vanadium, cesium, beryllium, magnesium, calcium, chromium, molybdenum, silicon, germanium, aluminum, iridium, nickel, palladium, platinum, iron, copper, titanium, tungsten, silver, gold, zinc, cadmium, indium tin oxide, carbon, and carbon nanotube.

175. (New) The molecular sensing apparatus of claim 166 wherein at least one of said first electrode and said second electrode is functionalized with a chemical group that can be derivatized or crosslinked.

176. (New) The molecular sensing apparatus of claim 175 wherein said chemical group is a sulfate, a sulfhydryl, an amine, an aldehyde, a carboxylic acid, a phosphate, a phosphonate,

an alkene, an alkyne, a hydroxyl, a bromine, an iodine, a chlorine, a light-activatable group, or a group activatable by an electric potential.

177. (New) The molecular sensing apparatus of claim 166 wherein at least one of said first electrode and said second electrode is coated with a self-assembled monolayer.

178. (New) The molecular sensing apparatus of claim 177 wherein said self-assembled monolayer comprises a compound selected from the group consisting of an alkanethiol, a phospholipid, a bola amphiphile, and an oligo(phenylenevinylene).

179. (New) The molecular sensing apparatus of claim 168 wherein the biological macromolecule is attached to the first electrode by a thiol group.

180. (New) The molecular sensing apparatus of claim 168 wherein the biological macromolecule is attached to the first electrode by a phosphonate.

181. (New) The molecular sensing apparatus of claim 168 wherein the biological macromolecule is attached to said first electrode by a linker.

182. (New) The molecular sensing apparatus of claim 181 wherein said linker is selected from the group consisting of DFDNB, DST, ABH, ANB-NOS, EDC, NHS-ASA, and SIA.

183. (New) The molecular sensing apparatus of claim 166 wherein the first electrode has a first surface and the second electrode has a second surface, and wherein the first surface is not coplanar to the second surface.

184. (New) The molecular sensing apparatus of claim 166 wherein said one or more electrode pairs comprise at least three electrode pairs.

185. (New) The molecular sensing apparatus of claim 166 wherein said one or more electrode pairs comprise at least 10,000 electrode pairs.

186. (New) The molecular sensing apparatus of claim 166 wherein said one or more electrode pairs comprises $10^2$ to $10^{10}$ electrode pairs.

187. (New) The molecular sensing apparatus of claim 166 the apparatus further comprising a measurement device electrically coupled to the first electrode and to the second electrode said first electrode pair.

188. (New) The molecular sensing apparatus of claim 187 wherein said measurement device measures an electromagnetic property selected from the group consisting of direct electric current, alternating electric current, permitivity, resistivity, electron transfer, electron tunneling, electron hopping, electron transport, electron conductance, voltage, electrical impedance, signal loss, dissipation factor, resistance, capacitance, inductance, magnetic field, electrical potential, charge and magnetic potential.

189. (New) The molecular sensing apparatus of claim 166 further comprising an electrical circuit electrically coupled to the first electrode and the second electrode of said first electrode pair.

190. (New) The molecular sensing apparatus of claim 189 wherein said electrical circuit comprises an electric signal gating system.

191. (New) The molecular sensing apparatus of claim 166 wherein said biological molecule connects to said first electrode and said second electrode in said first electrode pair.

192. (New) The molecular sensing apparatus of claim 166 wherein

a first biological macromolecule is attached to said first electrode in said first electrode pair, and

a second biological macromolecule is attached to said second electrode in said first electrode pair.

193. (New) The molecular sensing apparatus of claim 166 further comprising a computer electrically coupled to the first electrode and the second electrode of at least one electrode pair in said one or more electrode pairs.

194. (New) The molecular sensing apparatus of claim 166 wherein at least one of the first electrode and the second electrode in an electrode pair in said one or more electrode pairs comprises a semiconductor material.

195. (New) The molecular sensing apparatus of claim 194 wherein said semiconductor material has a resistivity between $10^{-6}$ Ω-m and $10^{7}$ Ω-m.

196. (New) The molecular sensing apparatus of claim 194 wherein the semiconductor material is selected from the group consisting of silicon, dense silicon carbide, boron carbide, $Fe_3O_4$, germanium, silicon germanium, silcon carbide, tungsten carbide, titanium carbide, indium phosphide, gallium nitride, gallium phosphide, aluminum phosphide, aluminum arsenide, mercury cadmium telluride, tellurium, selenium, ZnS, ZnO, ZnSe, CdS, ZnTe, GaSe, CdSe, CdTe, GaAs, InP, GaSb, EnAs, Te, PbS, InSb, PbTe, PbSe, and tungsten disulfide.

197. (New) The molecular sensing apparatus of claim 1, wherein a biological macromolecule or macromolecule/analyte complex connects said first electrode and said second electrode in said first electrode pair.

198. (New) The molecular sensing apparatus of claim 197 wherein said biological macromolecule is selected from the group consisting of a nucleic acid, a protein, a polysaccharide, a lectin, and a sugar.

199. (New) The molecular sending apparatus of claim 197 wherein said biological macromolecule is a deoxyribonucleic acid or a nucleic acid.

200. (New) The molecular sensing apparatus of claim 197 wherein said biological macromolecule is functionalized with a chemical group selected from the group consisting of a sulfate, a sulfhydryl, an amine, an aldehyde, a carboxylic acid, a phosphate, a phosphonate, an alkene, an alkyne, a hydroxyl, a bromine, an iodine, a chlorine, a light-activatable group, and a group activatable by an electric potential.

201. (New) The molecular sensing apparatus of claim 197 wherein the biological macromolecule is attached to the first electrode by a thiol group.

202. (New) The molecular sensing apparatus of claim 197 wherein the biological macromolecule is attached to the first electrode by a phosphorothioate or a phosphonate.

203. (New) The molecular sensing apparatus of claim 197 wherein the biological macromolecule is attached to said first electrode by a linker.

204. (New) The molecular sensing apparatus of claim 203 wherein said linker is selected from the group consisting of DFDNB, DST, ABH, ANB-NOS, EDC, NHS-ASA, and SIA.

205. (New) The molecular sensing apparatus of claim 1 wherein a first biological macromolecule is attached to the first electrode and a second biological macromolecule is attached to the second electrode.

206. (New) The molecular sensing apparatus of claim 1 wherein said first electrode comprises a surface with a shape selected from the group consisting of convex, concave, textured, corrugated, patterned uniformly, and randomly patterned.

207. (New) The molecular sensing apparatus of claim 199 wherein said nucleic acid is deoxyribonucleic acid or ribonucleic acid.

## REMARKS

Claims 2-4, 16-19, and 40 have been canceled without prejudice. Applicants reserve the right to prosecute the subject matter of the canceled claims in the present application or in one or more continuation, continuation-in-part or divisional applications. Claims 1, 5-15, and 21-39 have been amended for clarity. Further, new claims 166-207 have been added to more particularly claim certain aspects of the present invention. Therefore, upon entry of the instant amendment, claims 1, 5-15, 20-39, and 41-207 will be pending in the present application.

Various typographical errors have been corrected in the specification. In addition, the recitation of claim 28, as originally filed, has been inserted into page 22 of the specification, at the end of paragraph 80. No new matter has been added by these amendments to the specification.

Claims 5-15, 20, 22-24, 26-33, and 36-39, 93 were amended to correct for antecedent basis. Claim 6 was additionally amended to correctly designate a trademark. Claims 1, 5-15, and 21-39 were amended to improve clarity and/or to correct typographical errors.

In addition to the amendments described above, claim 1 was amended to recite one or more electrode pairs, wherein at least one electrode pair in the one or more electrode pairs comprises a first electrode and a second electrode separated by a distance that would allow a biological macromolecule or biological macromolecule/analyte complex to connect the first electrode to the second electrode. Claim 1 was further amended to recite that a portion of the insulator is removed between the first electrode and the second electrode thereby forming a channel within the insulator.

Support for the amended claims and the new claims can be found in the specification as follows.

| Claim | Support in the specification |
|---|---|
| 1 | Paragraphs 55, 63, 76-78, 191, Figs. 6A-6C, Figs. 1, 2A, 2B, 3A, 3B, 4A, 4B, 5, and 13 |
| 9-10 | Paragraph 13 |
| 12 | Paragraphs 13 and 131 |
| 14 | Paragraph 13 |
| 26-28 | Paragraph 80 |
| 34-35 | Paragraph 19, 28 |

| Claim | Support in the specification |
|---|---|
| 166 | Paragraphs 75, 76, Fig 6B |
| 167 | Paragraph 54 |
| 168 | Paragraphs 54, 55 |
| 169 | Paragraph 56 |
| 170 | Paragraphs 33, 56, 101 |
| 171-172 | Paragraph 12 |
| 173-178 | Paragraph 13 |
| 179-182 | Paragraph 14 |
| 183 | Paragraph 15 |
| 184-185 | Paragraph 16 |
| 186 | Paragraph 80 (as amended to incorporate claim 28 as originally filed) |
| 187 | Paragraphs 144-155 |
| 188 | Paragraph 17 |
| 189-191 | Paragraphs 18, 144-155 |
| 192 | Paragraph 64, 75, 76, Figs. 2A and 2B |
| 193 | Paragraph 18 |
| 194-196 | Paragraph 20 |
| 197 | Paragraph 9 |
| 198-199 | Paragraph 57 |
| 200 | Paragraph 10 |
| 201-204 | Paragraph 14 |
| 205 | Paragraph 64 |
| 206 | Paragraph 15 |
| 207 | Paragraphs 33, 54, 55, and 101 |

The amendments do not, therefore, contain new matter.

## THE RESTRICTION REQUIREMENT

The Examiner has required restriction of the pending claims under 35 U.S.C. § 121 to one of the following three groups:

I. Claims 1-40, drawn to a molecular sensing apparatus, classified in class 422, subclass 82.01.

II. Claims 41-72, drawn to methods of making an apparatus, classified in class 422, subclass 68.1.

III. Claims 73-165, drawn to methods of analyte detection, classified in class 435, subclass 4.

The Examiner contends that the inventions of Groups I , II, and III are distinct, each from the other.

In order to be fully responsive, Applicants hereby elect to prosecute the invention of Group I, claims 1-40, drawn to a molecular sensing apparatus, classified in class 422, subclass 82.01. In addition to claims 1-40, Applicants believe that new claims 166-207 are also within the elected Group I. Applicants respectfully request that the above-made remarks be considered and made of record in the file history of the above-captioned application.

## CONCLUSION

If any fees are due in connection with this submission, please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150. A copy of this sheet is enclosed.

Respectfully submitted,

Date: August 20, 2003

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for
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Enclosures